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Limb-Sparing Treatment for Soft Tissue Sarcomas: Influence of Prognostic Factors

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At present, limb-sparing surgery is the most appropriate and acceptable treatment available for sarcomas of the extremities, although the right balance between conservative therapy and maximum efficacy has yet to be found. A better knowledge of prognostic factors may help in planning the appropriate strategy for each case. Eighty patients underwent limb-sparing surgery for limb sarcomas (17 had surgery alone; 19 had neo-adjuvant hyperthermic antiblastic perfusion combined or not with postoperative radiotherapy, and 44 had adjuvant radiotherapy). Univariate and multivariate analyses were made to detect statistically significant differences between subgroups and identify the more significant subset of prognostic factors. Only microscopically positive surgical margins were related to a greater risk of local recurrence, whereas overall survival was compromised by high grade and large tumor size. © 1996 Wiley-Liss, Inc.

KEY WORDS: **soft tissue sarcomas, limb-sparing surgery, locoregional treatment, prognosis**

INTRODUCTION

Limb-sparing surgery, either alone or combined with adjuvant high-dose radiotherapy and\or locoregional chemotherapy (i.e., intra-arterial infusion or perfusion), may be feasible in most patients with soft tissue sarcomas of the extremities. After treatment, local control is achieved in 70–90% of treated cases, and a 5-year survival of ~70% has been reported [1]. This therapeutical approach is quite complex because the right balance must be found between conservative therapy and maximum efficacy. The decisions made by the treatment teams, however, may now be facilitated by improvements in our understanding of factors affecting local control and survival in patients with limb sarcomas.

Recent reports in the literature show that positive surgical margins are the most important factor in local recurrence, whereas their significance as an independent determinant of survival is still widely debated, as is the prognostic importance of local recurrence [2–12]. Tumor grade and size, however, are commonly accepted as the most important factors affecting survival, whereas their role in local control of tumors is uncertain [4,8,9,11,13]. Findings on the prognostic value of other factors, such as age, sex, type of presentation, tumor site and location, or DNA characteristics, are contradictory [14].

Here, we evaluate factors influencing the outcome of treatment for soft tissue sarcomas of the extremities in 80 patients referred to our institute, with the aim of ascertaining their utility to multidisciplinary teams in providing the most conservative surgery possible.

MATERIALS AND METHODS

Patients

Our series consisted of 80 patients (40 F, 40 M; median age 53 years, range 18–89) who underwent limb-sparing surgery; of these, 17 had surgery alone, 19 had neo-adjuvant hyperthermic-antiblastic perfusion combined or not with postoperative radiotherapy, and 44 had adjuvant radiotherapy. A routine complete medical history was obtained from all patients, and physical examination, blood samples for routine serum chemistries, cell counts, and chest X-rays were performed. All patients underwent

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CT scan or MRI of the affected limb and CT scan of the lungs. Incisional biopsy was taken for histology in 48 (60%) cases, excisional biopsy in 26 (33%), and needle biopsy in 6 (7%). All histology specimens from other institutions were reviewed by the same pathologist. Histotypes were graded as well (G1), moderately (G2), or poorly (G3) differentiated. When in the final pathology report tumor cells were identified at the cut edge or closer than 1 mm to it, surgical margins were considered microscopically positive.

Hyperthermic Antiblastic Perfusion (HAP)

From 1989 through 1992, neo-adjuvant HAP with doxorubicin was given to 19 patients with primary or recurrent intermediate/high grade (G2-3) limb sarcomas that were >5 cm or extracompartmentally sited. None had received chemo and/or radiotherapy. Doxorubicin was administered at 0.7 or 1.4 mg/kg b.w. (upper or lower limb respectively), achieving a temperature of 40.5–42°C at the tumor site, under limb isolation perfusion. Locoregional toxicity was evaluated according to Wieberdink's criteria [15]. All patients underwent limb-sparing surgery within 4–6 weeks from perfusion. When tumor resection was marginal (7 patients), external beam irradiation was undertaken postoperatively.

Surgery

Limb-sparing surgery consisted of the following types of resection: *intralesional,* when macroscopic tumor deposits were left (2 patients); *marginal,* if closer than 1 cm to tumor pseudocapsule with no evidence of macroscopic residues (29 patients); *wide,* when excised tumor was entirely surrounded by a cuff of normal tissue thicker than 1 cm (44 patients); and *radical,* with complete removal of the lesion along with the muscular compartment (5 patients). Limb-sparing surgery alone was considered adequate in 17 patients (i.e., after compartmental resection or wide excision when tumors were smaller than 5 cm).

Radiotherapy

Adjuvant radiotherapy was given after intralesional and marginal resection. Forty-four patients underwent external beam irradiation (megavoltage photon or electron) after surgery alone and 7 after neo-adjuvant HAP and surgery, with a median total dose of 57 Gy (range 41–70) in a single daily fraction of 180–200 cGy, 5 times a week, administered with a shrinking-field technique. To minimize morbidity, a strip of normal nonirradiated tissue was preserved.

Follow-Up

Close clinical follow-up, pursued every 4 months for the first 2 years after local treatment and every 6 months thereafter, consisted of physical examination, chest X-rays, CT scans of the chest and upper abdomen, MRI or CT scan of the affected limb. No patients were lost to follow-up (median 36 months, range 12–154).

TABLE I. Distribution of Limb Sarcomas by Histologic Type and Grade

Histologic type	N (%)	G1 N (%)	G2 N (%)	G3 N (%)
MFH[a]	24 (30)	3 (12)	5 (21)	16 (67)
Liposarcoma	21 (26)	13 (62)	2 (10)	6 (32)
Leiomyosarcoma	14 (18)	3 (21)	5 (36)	6 (43)
Synovial sarcoma	6 (7)	2 (33)	—	4 (67)
MPNST[b]	5 (6)	—	4 (80)	1 (20)
Clear cell sarcoma	3 (4)	—	—	3 (100)
Angiosarcoma	3 (4)	—	—	3 (100)
Others	4 (5)	3 (75)	—	1 (25)
Total	80 (100)	24 (30)	16 (20)	40 (50)

[a]Malignant fibrous histiocytoma.
[b]Malignant peripheral nerve sheath tumor.
N = number of patients.

Statistical Analysis

Cumulative proportion survival and local recurrence-free interval curves were analyzed according to Kaplan-Meier's method from the date of diagnosis to local recurrence development or death, respectively. To detect statistical differences between subgroups, the log-rank test (Mantel-Cox) was used at univariate analysis. Multivariate analysis was performed using the Cox model. Stepwise regression based on the same model was, moreover, used to identify the more significant subset of risk factors. All analyses were performed using the BMDP statistical package for PC.

RESULTS

Patients and Tumor Characteristics

At presentation, 66 (82.5%) patients had primary tumors and 14 (17.5%) local recurrences. Twenty-two (27.5%) tumors were localized in the upper limb (2 in the hand or wrist), and 58 (72.5%) in the lower limb (4 in the foot or ankle). Sixty (75%) had a proximal and 20 (25%) a distal location; 54 (67.5%) tumors were intracompartmental; 26 (32.5%) were extracompartmental. The median duration of symptoms for primary sarcomas was 18 months (range 2–74).

Tumor violation occurred in five cases and overall surgical margins were positive in 15 (3 with cells within 1 mm). Histologic types and tumor grade are listed in Table I. The median tumor size was 10.5 cm (range 3–28).

Local morbidity after HAP was G1-2 (mild erythema and/or edema) in 14 and G3 (considerable erythema and edema, blistering and slight motility impairment) in three patients, two of whom developed deep venous thrombosis. Only one patient had permanent sensory-motor nerve impairment (G4). Complications after limb-sparing surgery, recorded in 24 patients, were mainly wound-healing

related and were treated on an out-patient basis. Surgical drainage was required for a hematoma in one patient and for an abscess in two patients.

Pattern of Disease Recurrence

Following limb-sparing surgery, 18 (23%) patients had local recurrences after a median time of 13 months (range 2–51), 15 (22%) of these were among the 66 patients who presented a primary tumor at initial treatment, and 3 (21%) were among the 14 with a local recurrence. The two patients who underwent intralesional resection were considered disease-free at the end of the whole treatment. This consisted of surgery and high-dose radiotherapy (68) for the first and surgery followed by high-dose radiotherapy (70 Gy) and i.v. doxorubicin (6 cycles) for the second patient. The former, treated for a very large (18 cm) lipomixoid sarcoma of the proximal thigh, is still alive and disease-free after 6 years, whereas the second, who had MFH (Grade 3) of the elbow, did not develop local recurrence, but died of distant multiple metastases at 9 months.

Local recurrences occurred in 4 (23%) out of 17 patients treated with adequate surgery alone. In these patients, one compartmentectomy and three wide resections with external beam radiotherapy were performed.

Of 10 patients (22%) who had local relapse after surgery and external beam adjuvant radiotherapy, five underwent amputation, three marginal resection and brachytherapy, and another two were given systemic chemotherapy for synchronous distant metastases.

Of the 19 patients who had HAP and surgery combined with or without external beam irradiation, four (21%) had local recurrences; two of these underwent amputation, one had a marginal resection and re-irradiation, and the remaining one had local excision and systemic chemotherapy for distant metastases. Regarding the status of surgical margins, local recurrence occurred in 9 (60%) out of 15 margin positive and in 9 (13%) out of 65% margin negative patients ($P = 0.0003$).

None of the seven patients who had salvage amputation (limb salvage rate 91%) had local recurrences, whereas two of the eight who had limb-sparing surgery and radiotherapy for local recurrence had local re-recurrence and distant metastases, and no further surgery was attempted.

Of the 18 patients who developed local recurrences, two had distant synchronous metastases, and three had distant metastases after local recurrence. Thirteen patients are alive after surgery for local recurrences, with a median follow-up of 28 months (range 8–96). Five died after a median period of 5 months (range 2–19).

Of the 62 patients without local recurrence, 19 developed distant metastases, 46 are alive, 2 after salvage resection for pulmonary metastases and systemic chemotherapy, and 1 after liver resection and chemotherapy. The overall median survival was 47 months (range 14–149). Eighteen patients died of distant metastases after a median interval of 7 months (range 3–22).

Statistical Analysis

Local control. Cumulative proportion 5-year local disease-free survival is 67.5%. At univariate analysis (Table II), the only prognostic factor found to have a significant influence was surgical margins ($P = 0.0003$). The Cox regression model for local recurrence was highly significant ($P = 0.006$), although only the margins coefficient ($P < 0.001$) was of statistical significance. This finding was confirmed by stepwise regression, which identified this variable as the most significant.

Survival. Cumulative proportion 5-year overall survival was 65%. Univariate analysis (Table II) revealed significant values only for size ($P = 0.003$), grade ($P = 0.03$), and neo-adjuvant HAP ($P = 0.004$), but surgical margins and local failure were of borderline significance ($P = 0.06$). The regression model was highly significant ($P = 0.002$), but only size class ($P = 0.02$) achieved the level of significance. Stepwise regression identified size and grade as the more independent variables (Table III). Since HAP was given to patients with high grade and locally advanced sarcomas, its borderline significance in the final model may have been due to a close correlation with grade and size and the particular process of stepwise regression in selecting the variables.

DISCUSSION

Over the last 20 years, limb-sparing surgery has almost completely replaced amputation for sarcomas of the extremities. Two factors have greatly contributed to this development: improvement in locoregional adjuvant therapies and an improved understanding of the natural history of these tumors.

Today, small (<5 cm) and superficial sarcomas require simple resection with safe margins, irrespective of their grade of malignancy, whereas larger tumors often require adjuvant treatment (radiotherapy and/or locoregional chemotherapy), especially if they are high grade and deeply seated. Nevertheless, 15–20% of limb sarcomas still develop a local recurrence after apparently adequate treatment, and this percentage is 50–75% when surgery is inadequate and negative margins are not obtained. Moreover, the overall long-term survival of ~70% observed among these patients does not seem to be influenced by local treatment [1].

The above considerations can complicate decision making by multidisciplinary teams, and some fundamental questions regarding strategy for the care of limb soft tissue sarcomas are still unanswered. When, e.g., positive microscopic margins are found during conservative surgery, it is not always clear whether amputation is still advisable. This question ultimately will be answered only by long-term results from prospective randomized trials.

TABLE II. Cumulative Proportion 5-Year Local Disease-Free (CPDF) and Overall Survival (CPS) by Variable (Univariate Analysis)

Variable		No. patients	CPDF	P*	CPS	P*
Age	<50	31	67	0.53	79	0.19
	>50	49	72		65	
Sex	Male	40	77	0.70	61	0.40
	Female	40	65		73	
Presentation	Primary	66	72	0.66	67	0.42
	Recurrent	14	71		74	
Site	Upper l.	22	72	0.65	80	0.25
	Lower l.	58	69		64	
Location	Proximal	60	67	0.27	63	0.12
	Distal	20	82		82	
Compartmentality	Intra	54	70	0.89	68	0.92
	Extra	26	75		64	
Size (cm)	0–5	38	81		83	
	5–10	27	71	0.11	53	0.003
	>10	15	42		53	
Grade	Low	24	73		91	
	Intermediate			0.23		0.03
	High	56	72		57	
Neo-adjuvant HAP[a]	No	61	73	0.11	77	0.004
	Yes	19	65		39	
Surgical margins	Negative	65	79	0.0003	73	0.06
	Positive	15	26		42	
Local failure	No	62	—	—	71	0.06
	Yes	18			56	

[a]Hyperthermic antiblastic perfusion.
*Mantel-Cox.

TABLE III. Summary of Stepwise Analysis: Results for Overall Survival

Variable	DF[a]	Log likelihood	Improv. Chi-sq.[b]	P value
Size	1	−88.041	8.773	0.003
Grade	1	−84.092	7.899	0.005
HAP[c]	1	−80.450	3.129	0.077

[a]Degree of freedom.
[b]Improvement Chi-square.
[c]Hyperthermic antiblastic perfusion.

At present, decisions on therapeutical strategy are made difficult by our limited experience and the relatively few studies on margin status available in literature (Table IV). Most data reported confirm our results, showing that positive surgical margins play an important role in the prediction of local recurrence after limb-sparing surgery. Moreover, multivariate statistical analysis indicates that the status of surgical margins is the most important prognostic factor for local control [2,16]. Other factors analyzed for local control in the present study and in the literature were either of no statistical significance or yielded contradictory results: tumor grade is perhaps the most controversial [3,9,11,17].

In view of the negative influence of positive surgical margins on local control, amputation should be performed for 13–36% [2,3,13,18] of tumors with positive margins in patients undergoing limb-sparing surgery for soft tissue sarcomas, as well as in cases (5–10%) in which it is unavoidable because of tumoral spread or recurrence after multidisciplinary treatment [18]. However, despite the fact that patients with positive margins have a higher incidence of local recurrence, there is little agreement on the role of local failure in their prognosis.

Conflicting results have been reported on the influence of positive surgical margins on the overall 5-year survival of patients who have undergone limb-sparing surgery for limb sarcomas (Table IV) [19]. Likewise, the concept of local recurrence as a predictor of survival has been strongly debated and, at present, most authors sustain that this event has no measurable impact on survival [20,21]. Local recurrence ("persistence") after conservative treatment seems more likely to reflect a poor prognosis, not to cause it [12,17,22–25].

Williard and colleagues [26] observed better local control in patients who underwent amputation (94%) than in those treated with limb-sparing surgery (85%) for soft tissue sarcomas ($P = 0.007$), but the rate of distant metastases was much lower after conservative surgery (14%) than after amputation (43%) ($P = 0.000003$). By making a stratification for tumor grade and size of the two groups of patients, these authors also found that amputation had no advantage over local control and recommended the former only for the patients with tumors that cannot be

TABLE IV. Five-Year Local Control and Survival According to Status of Surgical Margins as Reported by Different Authors

Author (year) [ref]	Number of patients	5-year local control: Margin status Positive (%)	5-year local control: Margin status Negative (%)	5-year local control: *P* value	5-year survival: Margin status Positive (%)	5-year survival: Margin status Negative (%)	5-year survival: *P* value
Markhede et al. (1982) [8]	97	23[a]	94[a]	—	34–40	53–76	0.01
Potter et al. (1986) [2]	211	75	75	0.57	81	88	0.73
Collin et al. (1986/88) [3, 4]	423	45	68	0.004*	52	77	0.0001*
Suit et al. (1988) [5]	220	57–87	79–91	—	44–82[b]	50–91[b]	—
Stotter et al. (1990) [6]	175	20–60	90	0.01*	62–78	82–90	NS*
Fagundes et al. (1991) [7]	49	39–40	91	—	—	—	—
Herbert et al. (1993) [9]	77	55–80	100	0.03*	55–72	90	0.02*
Sadoski et al. (1993) [10]	132	82	97	0.02	—	—	—
Tanabe et al. (1994) [11]	95	62	91	0.008*	70	65	NS*

[a]No postoperative radiotherapy planned after marginal or radical surgery.
[b]Disease-free survival.
*Multivariate analysis.

grossly resected with a limb-sparing procedure while preserving a functional extremity [26]. However, although it has not been demontrated that local recurrences contribute to distant spread, it is generally agreed that every effort should be made to prevent them, as they cause the patient further suffering. Interesting results in this perspective seem to come from the recent experiences with conservative surgery associated to brachytherapy [27,28] and/or isolation perfusion with doxorubicin and/or TNF alpha [1,29].

At present, the only two prognostic factors that really seem to influence the long-term survival of patients with soft tissue sarcomas of the extremities are tumor dimension and grade. The cumulative proportion overall 5-year survivals were 43% and 57%, respectively, in our patients with a tumor diameter >10 cm or intermediate-high grade lesions. Similar results have recently been reported by other authors [2–11]. This observation implies that when they come to observation, most high risk tumors have already given rise to distant micrometastases, and this leads to another crucial question: has adjuvant systemic chemotherapy a role in therapy for soft tissue sarcomas of the limbs? As yet, no clear answer has been found, but a consideration of the most important prognostic factors may help prompt further research in this area. In fact, in the four randomized trials reported in the literature [30–33], it is noted that adjuvant systemic treatment arms have a statistically significant improvement in disease-free survival, whereas overall survival is significantly prolonged in only one study [30]. These trials, however, have been widely criticized for their methodological bias, such as patient number and selection and chemotherapy timing and/or dosage. In their recent retrospective analysis, Williard et al. [26] reported that adjuvant chemotherapy can improve survival after resection of high grade tumors measuring 10 cm or more ($P = 0.01$). Recently, two new prospective randomized trials were proposed in Europe (by the E.O.R.T.C. Soft Tissue and Bone Sarcoma Group) and in Italy (by the Rizzoli Institute). Both trials recruit only patients with high risk tumors with the aim of detecting any advantages in survival from high dose adjuvant chemotherapy (ifosfamide and doxorubicin with rh GM-CSF) over local treatment alone. Therefore, multidisciplinary teams involved in the treatment of soft tissue sarcomas should now plan to enroll as many patients as possible in such or similar studies with a view to clarifying the above issue.

In conclusion, advances made in the knowledge of prognostic factors in soft tissue sarcomas have greatly influenced the treatment of these rare tumors. Now amputation is usually performed only in patients for whom a limb-sparing procedure cannot preserve a sufficient limb function, and this is warranted irrespective of the status of surgical margins, since the persistence of a small tumor deposit after surgery does not seem to have any negative prognostic implication for the long-term survival of these patients. However, most of these patients have large and/or high grade tumors and the highly adverse impact on survival of these prognostic factors is well known. The hypothesis that adjuvant chemotherapy might be more effective in high risk patients and the introduction of new agents into combination chemotherapy have prompted new prospective randomized trials with the aim of demonstrating a significant survival advantage. Further advances in the knowledge of the biological behavior of soft tissue sarcomas are forthcoming from new investigational techniques applied to molecular biology. Hopefully, more detailed information should replace or flank traditional prognostic factors to help treatment teams tailor therapy for each patient.

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